



TTN gene

titin

Normal Function

The *TTN* gene provides instructions for making a very large protein called titin. This protein plays an important role in muscles the body uses for movement (skeletal muscles) and in heart (cardiac) muscle. Slightly different versions (called isoforms) of titin are made in different muscles.

Within muscle cells, titin is an essential component of structures called sarcomeres. Sarcomeres are the basic units of muscle contraction; they are made of proteins that generate the mechanical force needed for muscles to contract. Titin has several functions within sarcomeres. One of the protein's main jobs is to provide structure, flexibility, and stability to these cell structures. Titin interacts with other muscle proteins, including actin and myosin, to keep the components of sarcomeres in place as muscles contract and relax. Titin also contains a spring-like region that allows muscles to stretch. Additionally, researchers have found that titin plays a role in chemical signaling and in assembling new sarcomeres.

Health Conditions Related to Genetic Changes

centronuclear myopathy

At least 12 mutations in the *TTN* gene have been found to cause centronuclear myopathy, a condition that is characterized by muscle weakness (myopathy) in the skeletal muscles. Most of these mutations alter the way the gene's instructions are used to produce titin, resulting in production of an abnormal protein. The abnormal titin protein has reduced or altered activity in muscle cells. It is unclear how these mutations cause centronuclear myopathy, but it is likely that the altered protein cannot interact with other proteins in the sarcomere, leading to dysfunction of the sarcomere. Abnormal sarcomeres prevent muscle cells from contracting and relaxing normally, resulting in the muscle weakness that is characteristic of centronuclear myopathy.

early-onset myopathy with fatal cardiomyopathy

At least two mutations in the *TTN* gene have been identified in people with early-onset myopathy with fatal cardiomyopathy (EOMFC), an inherited muscle disease that affects both skeletal and cardiac muscle. These genetic changes occur near the end of the *TTN* gene and lead to the production of an abnormally short version of the titin protein. The defective protein disrupts the function of sarcomeres, preventing

skeletal and cardiac muscle from developing and working normally. These muscle abnormalities underlie the characteristic features of EOMFC, including skeletal muscle weakness and a form of heart disease called dilated cardiomyopathy.

familial dilated cardiomyopathy

More than 50 mutations in the *TTN* gene have been found to cause familial dilated cardiomyopathy, a condition that weakens and enlarges the heart, preventing it from pumping blood efficiently. Signs and symptoms of familial dilated cardiomyopathy typically begin in mid-adulthood and result in heart failure. *TTN* gene mutations account for approximately 20 percent of all cases of familial dilated cardiomyopathy. These mutations result in the production of an abnormally short titin protein. It is unclear how the altered protein causes familial dilated cardiomyopathy, but it likely impairs sarcomere function and disrupts chemical signaling. Changes in sarcomere function reduce the heart's ability to contract, weakening and thinning cardiac muscle and leading to the signs and symptoms of familial dilated cardiomyopathy.

familial hypertrophic cardiomyopathy

hereditary myopathy with early respiratory failure

At least one mutation in the *TTN* gene has been found to cause hereditary myopathy with early respiratory failure (HMERF), an inherited muscle disease that predominantly affects muscles close to the center of the body (proximal muscles) and muscles that are needed for breathing. The identified mutation changes a single protein building block (amino acid) in the titin protein. Specifically, it replaces the amino acid arginine with the amino acid tryptophan at protein position 279 (written as Arg279Trp or R279W). Studies suggest that this change disrupts titin's interactions with other proteins within sarcomeres and interferes with the protein's role in chemical signaling. Consequently, muscle fibers become damaged and weaken over time. It is unclear why these effects are usually limited to proximal muscles and muscles involved in breathing.

limb-girdle muscular dystrophy

At least one *TTN* gene mutation has been found to cause limb-girdle muscular dystrophy type 2J (LGMD2J). Limb-girdle muscular dystrophy is a group of related disorders characterized by weakness and wasting of skeletal muscles, particularly in the shoulders, hips, and limbs. LGMD2J is a type of limb-girdle muscular dystrophy that has been identified only in the Finnish population, and all affected individuals have had the same *TTN* gene mutation. This genetic change deletes several amino acids and replaces them with other amino acids near the end of the titin protein. This complex mutation is known as FINmaj. The FINmaj mutation may disrupt titin's interactions with other proteins that are needed for muscle contraction. Decreased

ability to contract causes muscles to weaken and waste away over time, resulting in the signs and symptoms of limb-girdle muscular dystrophy.

tibial muscular dystrophy

Several mutations in the *TTN* gene have been identified in people with tibial muscular dystrophy, a condition that primarily affects the muscles at the front of the lower leg. The FINmaj mutation, described above, has been found to cause tibial muscular dystrophy in all affected people of Finnish descent. Other *TTN* gene mutations cause tibial muscular dystrophy in non-Finnish European populations.

Researchers predict that the *TTN* gene mutations responsible for tibial muscular dystrophy, including FINmaj, alter the ability of the titin protein to interact with other proteins within sarcomeres. Mutations may also interfere with the protein's role in chemical signaling. These changes disrupt normal muscle contraction, which causes muscles to weaken and waste away over time. It is unclear why these effects are usually limited to muscles in the lower legs in tibial muscular dystrophy.

other disorders

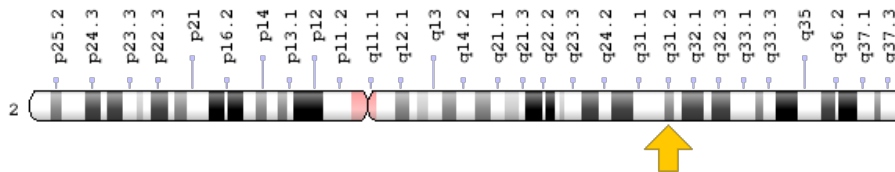
Mutations in the *TTN* gene can also cause a disorder of the cardiac muscle called familial hypertrophic cardiomyopathy type 9. Hypertrophic cardiomyopathy is a thickening of the cardiac muscle that forces the heart to work harder to pump blood. This condition is often associated with an abnormal heartbeat (arrhythmia) and can lead to heart failure and sudden death. Researchers have found at least three *TTN* gene mutations in people with familial hypertrophic cardiomyopathy type 9.

The mutations responsible for this heart condition likely disrupt the normal structure and function of titin. The genetic changes may alter titin's interactions with other muscle proteins or disrupt its role in chemical signaling. Researchers are working to determine why some conditions resulting from *TTN* gene mutations predominantly affect cardiac muscle, some predominantly affect skeletal muscle, and some affect both. They suspect that these differences may be related to the location of mutations in the *TTN* gene and the many varieties of titin that are produced in different muscles.

Chromosomal Location

Cytogenetic Location: 2q31.2, which is the long (q) arm of chromosome 2 at position 31.2

Molecular Location: base pairs 178,525,989 to 178,807,423 on chromosome 2 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- CMH9
- CMPD4
- CONNECTIN
- EOMFC
- FLJ32040
- LGMD2J
- MYLK5
- TITIN_HUMAN
- TMD

Additional Information & Resources

Educational Resources

- Molecular Biology of the Cell (fourth edition, 2002): Organization of Accessory Proteins in a Sarcomere (Figure)
<https://www.ncbi.nlm.nih.gov/books/NBK26888/?rendertype=figure&id=A3070>
- Molecular Cell Biology (fourth edition, 2000): Titin and Nebulin Filaments Organize the Sarcomere
<https://www.ncbi.nlm.nih.gov/books/NBK21670/#A5209>

GeneReviews

- Dilated Cardiomyopathy Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1309>
- Hereditary Myopathy with Early Respiratory Failure (HMERF)
<https://www.ncbi.nlm.nih.gov/books/NBK185330>
- Hypertrophic Cardiomyopathy Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1768>
- Limb-Girdle Muscular Dystrophy Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1408>
- Salih Myopathy
<https://www.ncbi.nlm.nih.gov/books/NBK83297>
- Udd Distal Myopathy
<https://www.ncbi.nlm.nih.gov/books/NBK1323>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28TTN%5BTIAB%5D%29+OR+%28titin%5BTIAB%5D%29+OR+%28connectin%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D>

OMIM

- TITIN
<http://omim.org/entry/188840>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_TTN.html
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=TTN%5Bgene%5D>
- HGNC Gene Family: Fibronectin type III domain containing
<http://www.genenames.org/cgi-bin/genefamilies/set/555>
- HGNC Gene Family: I-set domain containing
<http://www.genenames.org/cgi-bin/genefamilies/set/593>
- HGNC Gene Family: Immunoglobulin like domain containing
<http://www.genenames.org/cgi-bin/genefamilies/set/594>

- HGNC Gene Symbol Report
http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=12403
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/7273>
- UniProt
<http://www.uniprot.org/uniprot/Q8WZ42>

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